REMARKS

Claims 16-21, 23-28 and 30-21 are pending.

Claims 16-21, 23-28 and 30-21 have been rejected under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, as lacking a practical asserted utility. The Office Action states that the commercial value of such libraries does not have any bearing as to the utility requirement of the statute. Applicants respectfully submit that the libraries set forth in Claims 16-21, 23-28 and 30-21 meet the requirements of 35 U.S.C. 101 and 112 for utility.

The libraries of the invention provide a useful research tool for identifying molecular targets, *e.g.* in signaling pathways, and for providing amino acid sequences that interact with such targets. As described in the specification, and as demonstrated in the attached Declaration, libraries of a certain complexity will have screening value.

It is the assertion of Applicants that the collection of biomolecules in a library has a utility that is ***distinct*** from the utility of an individual peptide. An individual peptide cannot serve as a research tool for identifying targets, because it has a limited capacity for interaction. It is ***only*** when one has a collection of sufficient size and complexity that a group of individual peptides becomes a useful library.

The position of the Patent Office and the Courts supports Applicants assertion that libraries have a patentable utility. For example, as set forth in the MPEP 2107.01, it is stated that "Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a **clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds)**." (emphasis added).

As set forth in the MPEP, the claimed subject matter must have a specific and substantial utility. A "specific utility" is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. The presently claimed libraries have a specific utility. The libraries are useful in specific screening methods, such as those taught by Applicants, and are useful to identify molecular targets and biomolecules in cells.

The presently claimed libraries provide an experimentally proven resource for screening. A Declaration from Dr. Masuda, previously submitted in co-pending application 09/727,715, is attached herewith. The Declaration provides an explanation and statement as to the usefulness of the presently claimed libraries.

Several features of the claimed invention are important for this utility. One aspect is the retroviral vector, which transports the nucleic acid sequence into the cell, and provides the transcriptional elements for expression. Another aspect is the sequence encoding the candidate bioactive peptide, which is randomized as described in the specification, and which falls into a particular size class. A third aspect is the presence of the fusion partner, which provides additional functionality.

One of the most important aspects of the claimed invention is the complexity, which is recited to be at least 10^4 different sequences. The complexity allows one to have confidence that the library will provide for an interaction of interest.

A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. The presently claimed libraries have a substantial utility, because they provide a means of identifying specific compounds and targets.

Applicants acknowledge the Examiner's statement that "each case is treated on a case-to-case basis", and that the patentability of one library claim does not necessarily flow from the patentability of a different library claim. However, it is noted for the record that even in the last few weeks the Patent Office has issued claims reciting biochemical libraries of a scope and content similar to that of Applicants' claims. For example, a few recent patents include United States Patent 6,576,467, June 10, 2003; United States Patent 6,573,098, June 3, 2003; United States Patent 6,569,435, May 27, 2003; United States Patent 6,562,617, May 13, 2003; and United States Patent 6,562,576, May 13, 2003. Each of these patents specifically claims libraries, which claims have presumably have met the burden for patentability under 35 U.S.C. 101.

The Federal Circuit has recently emphasized the importance to biotechnology of patenting research tools. In *Integra Lifesciences I, Ltd. v. Merck KGaA* (Fed. Cir.) 02-1052, 02-1065, it was stated that "patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs." Even Judge Newman's dissent in this case maintained the importance of patenting research tools, stating that "A research tool is a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an assay kit, a laser device (as in Madey v. Duke University), or a biochemical method such as the PCR (polymerase chain reaction). It is as subject to the patent right as is any other device or method, whether it is used to conduct research or for any other purpose."

Judge Newman also made an important point regarding the distinction between a compound for research, and a research tool. A research tool, such as the presently claimed libraries, provides a means for important biological testing; and is distinct from a compound having certain specific properties that can be the subject of research.

Applicants respectfully submit that the presently claimed libraries meet the requirements of 35 U.S.C. 101, in that they possess a specific and substantial utility.

Claims 16-21, 23-38 and 30-31 have been rejected under 35 U.S.C. 112, first paragraph, as failing to provide a description of a nucleic acid where the candidate bioactive agent encodes a 100 amino acid residue with a randomized portion.

Applicants respectfully submit that one of skill in the art could practice the randomization of a peptide insert based on the teachings of the specification. The present invention provides methods and compositions to create, effectively introduce into cells and screen compounds that affect a signaling pathway. Little or no knowledge of the pathway is required, other than a presumed signaling event and an observable physiologic change in the target cell. The invention also provides for the isolation of the constituents of the pathway, the tools to characterize the pathway, and lead compounds for pharmaceutical development. By delivering the random sequences to cells and screening the same cells, without the need to collect or synthesize *in vitro* the candidate agents, highly efficient screening is accomplished. In addition, the present methods allow screening in the absence of significant prior characterization of the cellular defect *per se*.

As set forth on page 19, line 30 to page 20, line 9 of the application, "The candidate bioactive agents and candidate nucleic acids are randomized, either fully randomized or they are biased in their randomization, e.g. in nucleotide/residue frequency generally or per position. By "randomized" or grammatical equivalents herein is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively. As is more fully described below, the candidate nucleic acids which give rise to the candidate expression products are chemically synthesized, and thus may incorporate any nucleotide at any position. Thus, when the candidate nucleic acids are expressed to form peptides, any amino acid residue may be incorporated at any position. The synthetic process can be designed to generate randomized nucleic acids, to allow the formation of all or most of the possible combinations over the length of the nucleic acid, thus forming a library of randomized candidate nucleic acids."

The specification further provides guidance (page 21, lines 11-19) that "in one embodiment, the library is fully randomized, with no sequence preferences or constants at any position. In a preferred embodiment, the library is biased. That is, some positions within the sequence are either

held constant, or are selected from a limited number of possibilities. For example, in a preferred embodiment, the nucleotides or amino acid residues are randomized within a defined class, for example, of hydrophobic amino acids, hydrophilic residues, sterically biased (either small or large) residues, towards the creation of cysteines, for cross-linking, prolines for SH-3 domains, serines, threonines, tyrosines or histidines for phosphorylation sites, etc., or to purines, etc."

One of skill in the art could readily synthesize randomized molecular libraries encoding peptides of from 4 to 100 amino acids in length, using methods known in the art. Such methods are demonstrated in the Examples; see page 56, line 24 to page 57, line 7; and page 61, lines 5-23.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112. Withdrawal of the rejection is requested.

Claims 16-21, 23-28 and 30-31 have been rejected under 35 U.S.C. 112, second paragraph. The Office Action states that the term "encodes" is unclear in a composition claim. Applicants respectfully submit that the term "encodes" is perfectly clear to one of skill in the art. In fact, a quick search of issued patents shows that **6865** gene-related patents contain the claim word "encodes", used as Applicants have used the term. A few examples will suffice:

- U.S. 6,608,245: 1. A purified and isolated polynucleotide, the expression of which in a plant confers on said plant resistance to at least one Verticillium species, wherein said polynucleotide ***encodes*** a polypeptide comprising the amino acid sequence depicted in SEQ ID NO: 4.
- U.S. 6,608,182 13. An isolated polynucleotide which ***encodes*** a polypeptide comprising amino acids 85 to 165 of SEQ ID NO:2, wherein said polypeptide has VEGF2 activity.
- U.S. 6,608,037 3. The nucleic acid construct of claim 1 or 2 wherein the expressible gene ***encodes*** a toxin or a prodrug activating enzyme.

Applicants respectfully submit that one of skill in the art can readily determine the meaning of the present claims, that Applicants claim a library of nucleic acids, and such nucleic acids encode polypeptides having certain properties.

The claim term "insertion" is stated to be a method claim step. Applicants respectfully submit that the term "insertion" is a noun, as evidenced by the Merriam Webster Dictionary, having the definition:

Main Entry: **in·ser·tion**

Function: *noun*
1 : something that is inserted : as **a :** the part of a muscle that inserts **b :** the mode or place of attachment of an organ or part **c :** embroidery or needlework inserted as ornament between two pieces of fabric **d :** a section of genetic material that is inserted into an existing gene sequence.

In the context of the present claim, clearly dictionary definition **d** is relevant. The candidate peptide is not inserted into the retrovirus, the retrovirus comprises an insertion of genetic material (i.e. nucleic acid sequence that encodes a candidate bioactive peptide). The insertion of genetic material into retroviral vectors is well-known. For example, the textbook "Retroviruses"; John M. Coffin; Stephen H. Hughes;Harold E. Varmus 1997. Cold Spring Harbor Laboratory Press, describes in great detail the use of retroviral vectors. Clearly, retroviral function is not destroyed by the insertion of exogenous nucleic acid sequences.

The Office Action states that claims 23-25 are confusing because the added material (a fusion partner) relates to a process step, and does not further limit the base claim. Applicants respectfully submit that claims 23-25 meet the requirements of 35 U.S.C. 112.

The term "fusion protein" is a noun describing a particular type of protein that is known and used in the art. The term is defined as:

> fusion protein
> <protein> Protein formed by expression of a hybrid gene made by combining two gene sequences. Typically this is accomplished by cloning a cDNA into an expression vector in frame with an existing gene, perhaps encoding for example beta galactosidase[1].

Applicants respectfully submit that one of skill in the art would understand the claim term "nucleic acid sequences further encode a fusion partner translationally fused to said nucleic acid sequence" to refer to the characterization of a nucleic acid sequence. The nucleic acid sequence is being characterized by the polypeptide sequence that it encodes. The nucleic acid sequence encodes a candidate bioactive peptide. The nucleic acid sequence also encodes a fusion partner polypeptide. The fusion partner coding sequence and the candidate bioactive peptide coding sequence are arranged, such that the two are translationally fused.

Applicants further submit that dependent claims 23-25 are proper dependent claims. As set forth in M.P.E.P. 608.01(n) III,

> The test as to whether a claim is a proper dependent claim is that it shall

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1 Published at the Dept. of Medical Oncology, University of Newcastle upon Tyne

> include every limitation of the claim from which it depends (35 U.S.C. 112, fourth paragraph) or in other words that it shall not conceivably be infringed by anything which would not also infringe the basic claim.
>
> A dependent claim does not lack compliance with 35 U.S.C. 112, fourth paragraph, simply because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends. The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. 112 is whether the dependent claim includes every limitation of the claim from which it depends. The test is not one of whether the claims differ in scope.

Base claim 16 recites a library of retroviral nucleic acid sequences. Dependent claim 23 recites the library of nucleic acid sequences, wherein the nucleic acid sequence is further limited by the requirement that it encode a fusion partner. Every composition that infringes claim 23 would also infringe claim 16. Applicants respectfully submit that claims 23-25 are proper dependent claims. Withdrawal of the rejection is requested.

The Office Action states that it is not clear how a candidate bioactive peptide is considered intracellular. Applicants respectfully submit that the claims are directed to library of cells, wherein the cells comprise distinct nucleic acid sequences. The nucleic acid sequences oncode polypeptides, which are expressed intracellularly. Since Applicants are claiming a cellular composition, the candidate peptide can be intracellular.

In view of the above remarks, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. 112, second paragraph.

Claims 16-21, 23-28 and 30-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 47-50, and 53 of copending application 09/918,601 or claims 23-26 and 31-38 of copending application 727,715. Applicants respectfully submit that a provisional rejection of this type is properly addressed by allowance of one application, in the absence of other outstanding rejections, at which time a determination of double-patenting can be made based on the issued claims.

Claims 23-27 and 30-31 have been rejected under 35 U.S.C. 103 as unpatentable over Jenkins et al. (1995) EMBO J. in view of Nilsson (Current Opinions in Structural Biology, 1992). Jenkins reports combining retroviral expression cloning with random mutagenesis to identify two activating point mutations in the common signal-transducing subunit (h beta c) of the receptors for human granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5 by

virtue of their ability to confer factor independence on the haemopoietic cell line, FDC-P1. Kamb reports the use of GFP as a reporter gene.

Applicants respectfully submit that the presently claimed invention is not suggested or made obvious by the cited combination of references. Jenkins would not be motivated to insert a randomized sequence of 4 to 100 amino acids into sequences encoding receptors for human granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5. The screening methods taught by Jenkins *et al.* are directed to a specific biological assay, where a receptor is activated by a point mutation. It is extremely unlikely, if not impossible, that insertion of a randomized sequence of from 4 to 100 amino acids would result in specific activation of a receptor.

The libraries of the present invention may be imagined as analogous to antibody coding sequences, where the diversity of random sequence combinations ensures that virtually any polypeptide will have a cognate molecule that interacts with it. One would not expect such a randomized library to result in specific enzymatic or signal transducing activities. Rather, one would expect such a library to provide biomolecules that *interact* with proteins having, for example, specific enzymatic or signal transducing activities.

The methods of Jenkins *et al.* cannot rationally be extrapolated to the methods of the present invention, because Jenkins is directed to single base pair mutations that would result in a small, specific change in a particular activity. The diverse, randomized peptides of the present invention are not suggested by such methods.

The secondary reference does not remedy the deficiencies of the primary reference. Nilsson *et al.* teaches general methods relating to fusion proteins, but does not disclose a library as defined by the present claims, and therefore fails to suggest the present invention.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 103. Withdrawal of the rejection is requested.

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

If the Examiner finds that a Telephone Conference would expedite prosecution of this application, she is invited to contact the undersigned (650) 327-3400.

In the event that the transmittal letter is separated from this document and the Patent Office determines that extensions or other relief is required and/or fees are due applicants, the Applicant petitions for any required relief, including extensions of time, and authorize the Commissioner to charge our Deposit Account No. 50-0815, Order Number RIGL-004DIV, for any fees due in connection with the filing of this document. The Patent Office is not authorized to charge issue fees to our Deposit Account.

Respectfully submitted,
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Date: Sept. 5, 2003

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